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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/523,809 | 03/13/2000 | Michael P. Murphy | 686.03.498CON | 6553 |

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| EXAMINER | |
|---|---|
| KAUSHAL, SUMESH | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding..

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/523,809 | MURPHY ET AL. | |
| | Examiner | Art Unit | |
| | Sumesh Kaushal Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *31-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response filed on 04/08/05 has been acknowledged.

*Claims 1-30 are canceled.*
*Claims 65-71are newly filed.*
*Claims 31-70 are pending and are examined in this office action.*

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is* ***571-273-8300.***

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/8/05 has been entered.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of Invention:**

Invention relates to an artificial skin construct.

**Breadth of Claims and Guidance Provided in the Specification**

The scope of instant claims encompasses a cultured skin construct having at least two layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined i.e. the support on which the cell are cultured)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer, wherein the epidermal cell layer is multilayered, stratified, differentiated and exhibits a basal layer, suprabasal layer, a granular layer and a stratum corneum; and wherein the bilayered cultured skin construct has a basement membrane present at the junction of the first and second layers (*wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions).*

The scope of instant claims encompasses further encompasses a cultured skin construct having at least two layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined, i.e. the support on which the cell are cultured)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer *wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions).*

The scope of invention further encompasses a cultured skin construct having at least three layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer (*wherein the keratinocyte cells makes an epidermal layer (as*

*claimed) under any and all culture conditions: i.e. growth factors and culture conditions)* c) and a third layer of cells deposed on the second layer.

In addition the scope of invention as claimed encompasses method of producing and using the above mentioned skin construct for transplantation or implantation into a patient.

Even though the specification teaches optimization of culture conditions for human fibroblasts to produce a layer of extracellular matrix in the absence of exogenous matrix components (see spec. Examples 1, 3 and 15), the specification fails to disclose what are the culturing conditions i.e. culture media contents, growth factors, culture environment that leads to the synthesis of (i) type I and type III collagen, (ii) decorin, (iii) fibronectin, (iv) tenascin, and, (v) glycosaminoglycans. Specifically, the specification fails to disclose a culturing condition (culture media contents, growth factors, culture environment) in which the fibroblast cells when cultured produce type I and type III collagens (as claimed) and tenascin. The specification fails to identify type I and type III collagens (as claimed) and tenascin in the extracellular matrix secreted by cultured fibroblasts. In addition the specification fails to disclose that fibroblast cells derived form tissues selected from form tendon, lung, cartilage, urethra, corneal stroma, oral mucosa, umbilical cord, and intestine are capable of synthesizing extracellular components (as claimed) under any and all culture conditions. Regarding formation of an epidermal layer the specification only disclosed the use of a specific culture conditions, which comprises culturing the seeded keratinocytes in an epidermalization medium followed by culturing of the skin construct under submerged conditions (air-liquid interface) in a culture media that is different from the epidermalization medium (Spec. page 46, example-16). The specification fails to disclose that use of any and all culture conditions (i.e. culture media contents, growth factors, culture environment) would lead to the formation of an epidermal layer (as claimed) in a cultured skin construct.

**State of Art and Predictability**

The state of the tissue engineering art at the time of filing teaches that to engineer living tissues in vitro, cultured cells are coaxed to grow on bioactive

degradable scaffolds that provide the physical and chemical cues to guide their differentiation and assembly into three-dimensional tissues. The assembly of cells into tissues is a highly orchestrated set of events that requires time scales ranging from seconds to weeks and dimensions ranging from 0.0001 to 10 cm. Coaxing cells to form tissues in a reliable manner is the quintessential engineering design problem that must be accomplished under the classical engineering constraints of reliability. Even though fewer than five engineered tissues have been approved, there are still many technical challenges to overcome before an "off-the-shelf" tissue could be created that represent the translation of scientific discoveries into treatments for patients. Furthermore, the successful large-scale production of engineered tissues requires an adequate source of healthy expandable cells, the optimization of scaffolds, and the creation of bioreactors, which mimic the environment of the body and that are amenable to scale-up. Additional challenges include the preservation of the product so that it has a long shelf-life and the successful use of various approaches to prevent tissue rejection (Naughton et al Science 295:1009-1014, 2002, ref of record).

Under the law Limitations appearing in the specification but not recited in the claim are not read into the claim. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Furthermore, claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims. Raytheon Co. v. Roper Corp., 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984). See also MPEP § 2111 - § 2111.01. In instant case the invention as claimed encompasses multi-layered cultured skin construct comprising a layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during any and all culturing conditions. The instant claims fail to recite what are the culturing conditions for example culture media contents, growth factors, culture environment that leads to the synthesis of the claimed extracellular matrix components (I and type III collagens, decorin, fibronectin, tenascin and any and all glycosaminoglycans to support the growth and proliferation of second layer of epithelial cells. Similarly the instant claims fail to recite what are the

culturing conditions (culture media contents, growth factors, culture environment that leads to the formation of epidermis during any and all culturing conditions.

***Response to arguments***

The applicant argues that the fact that the experimentation may be complex does not necessarily make it undue if art is typically engage in such experimentation. The applicant argues that the specification does teach one skilled in the art to how to make and use the invention without undue amount of experimentation. The applicant argues that the specification does teach one of skill in the art how to make the claimed invention by disclosing disclosing various sources of fibroblast cell strains, teaching suitable vessels and growth surfaces, teaching culture media formulations describing environmental conditions, teaching seeding and culturing the fibroblasts in order to obtain a layer of cultured fibroblasts and extracellular matrix and teaching application of an epithelial cell layer to the construct. The applicant argues that the specificaiton fully enabled the invention as claimed because it teaches how to make and use the claimed invention without undue experimentation.

However, applicant's arguments are found NOT persuasive. The invention as claimed encompasses multi-layered cultured skin construct comprising a layer of cultured dermal fibroblast cells, which produce a layer of extracellular matrix in the absence of exogenous matrix components during any and all culturing conditions. The invention as claimed fails to recite what are the culturing conditions for example culture media contents, growth factors, culture environment that leads to the synthesis of the claimed extracellular matrix components (I and type III collagens, decorin, fibronectin, tenascin and any and all glycosaminoglycans to support the growth and proliferation of second layer of epithelial cells. Similarly the instant claims fail to recite what are the culturing conditions (culture media contents, growth factors, culture environment that leads to the formation of epidermis during any and all culturing conditions. The earlier office action clearly provided the evidence that the assembly of cells into tissues is a highly orchestrated set of events that requires time scales ranging from seconds to weeks and dimensions ranging from 0.0001 to 10 cm. Coaxing cells to form tissues in a reliable manner is the quintessential engineering design problem that must be

accomplished under the classical engineering constraints of reliability (see Naughton et al Science 295:1009-1014, 2002). Therefore defining culture conditions and a chemically defined medium required for each step involved in the development of cultured skin construct is considered essential practice the instant invention. Even though the specification discloses various chemically defined medias like growth medium, production medium, epidermalization medium, cornification medium, maintenance medium, chemically defined medium, seed medium, and other medias it is unclear which media is used at each step during the development of the cultured skin construct as claimed.

Under the law, the disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In instant case making a multi-layered cultured skin construct under any and all culture conditions (culture media contents, growth factors, culture environment) is not routine in the art and without sufficient guidance to a specific culture conditions the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 31-32, 36-38, 48-49, 53-56, 61-66 and 68-70 are rejected under 35 U.S.C. 102(e) as being anticipated by Lam et al (US 6,733,530, 2004).

The instant claims are drawn to a cultured skin construct having at least two layers, comprising: a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix and a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer.

Lam et al teaches an artificial skin construct for grafting onto a human patient, wherein the material comprising a composite of a biosynthetic substratum a layer of viable human dermal fibroblasts upon an upper side of the biosynthetic substratum and a layer of viable human keratinocytes over the dermal fibroblasts upon the upper side of the substratum (fig-1A-C, col.10, lines 60-67, col.11, lines 1-19)). The cited art further teaches a method for fabricating the composite material includes the application of dermal fibroblasts onto the substratum as a feeder layer and then inoculating autologous keratinocytes on the resultant structure (col.3, lines 36-48, col.11-12). The cited art further teaches that the fibroblasts were stimulated to produce collagen and other proteins by feeding the fibroblasts with DMEM supplemented with 10% FBS and ascorbic acid. The cited art further teaches culturing the skin construct in the presence of insulin, epidermal growth factor (EGF) and insulin (col. 6, lines 50-63). The cited art further teaches that fibroblast produces the basal proteins including the early basement membrane proteins such as collagen IV and fibronectin (col.4, lines 6-34). The cited art teaches the use of that the biosynthetic substratum membrane which is porous in nature as it comprise holes for fluid exchange (fig-3, col. 12, lines 17-24).

Furthermore the invention is draw to a product by process wherein the product obtained by the process as claimed is indistinguishable form the product obtained in the cited art. The MPEP clearly states that the claims define the property rights provided by a patent, and thus require careful scrutiny. The goal of claim analysis is to identify the boundaries of the protection sought by the applicant and to understand how the claims relate to and define what the applicant has indicated is the invention. See *In re Hiniker Co., 150 F.3d 1362, 1369, 47 USPQ2d 1523, 1529 (Fed. Cir. 1998, MPEP 2106 Sec. II C)*. Furthermore, preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. *See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951)*. In addition, if the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. *See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963)*. In instant case the bilayered skin construct as disclose in the prior art of record clearly anticipate the invention as claimed.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-35, 39-47, 50-52, 57-60, 67 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al (US 6,733,530, 2004 as applied to

claims 31-32, 36-38, 48-49, 53-56, 61-66, 68-70 above, and further in view of Naughton et al (US 5,266,480, 1993, ref of record).

The instant claims are drawn to a cultured skin construct having at least three layers, comprising: a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix and a second layer of epithelial cells (keratinocytes) disposed on the first layer to form an epidermal cell layer, and a third layer of cells diposed on the second layer of epithelial cells. The instant claims are further drawn to fibroblast cells that are genetically engineered. The instant claims are further drawn to a skin construct containing dermal papilla of hair follicles. The claims are further drawn to a method for transplantation or implantation of cultured skin construct in a patient.

As stated above Lam et al teaches an artificial skin construct for grafting onto a human patient, wherein the material comprising a composite of a biosynthetic substratum a layer of viable human dermal fibroblasts upon an upper side of the biosynthetic substratum and a layer of viable human keratinocytes over the dermal fibroblasts upon the upper side of the substratum. However Lam does not teaches a third layer of cells deposited on the second layer of epithelial cells. In addition Fleishmajer does not teaches genetic motification of cell in keratinocytes-fibroblast co-culture model or a skin construct containing a dermal papilla of hair follicles.

Naughton et al teaches a three-dimensional skin culture system. Regarding genetically engineered cells the cited art teaches genetic modification of cells used in the three-dimensional culture system to produce a foreign gene product selected from a growth factor, regulatory factor, peptide, hormone, antibody etc (co.20 lies 54-62). Regarding three layered skin construct the cited art teaches a culture of isolated fibroblasts was established on a nylon mesh, which resulted in the adherent and growth of fibroblasts into the meshwork. The cited art teaches that these fibroblasts were metabolically active, secreted an extracellular matrix, and rapidly formed a dermal equivalent consisting of active fibroblasts and collagen (type I any type III) see col.44 lines 20-35. The cited art further teaches that melanocytes (second layer) were plated on to the fibroblast coated nylon mesh and allowed to grow for 3 days prior to the addition of keratinocytes (third layer) see col.45 lines 1-14. In addition the cited art

teaches that other types of cells that may be used to inoculate the three-dimensional matrix include endothelial cells, pericytes, macrophages, monocytes, lymphocytes, plasma cells adipocytes etc (col. 30 line 53-59). Regarding hair follicles the cited art teaches three-dimensional skin culture system may include introduction of a hair follicles and associated glands into the transplant site. The cited art further teaches implantation of skin-constructs containing hair follicles thereby creating a transplanted site, which is histologically normal and functionally similar to the normal skin (col.31, lines 44-59). Regarding method of transplanting the cited art teaches a method for transplantation or implanting of cultured skin construct in-vivo (col.45, line 40). The cited art teaches transplantation of skin construct in experimental rats, wherein meshes with dermal and epidermal components were implanted into 10mmx10mm skin biopsies. The cited art further teaches that these engraftment studies suggested that the three-dimensional skin matrix system mimics a true physiological system in which all cell components are activated and natural growth factors are being produced (col. 46 lines 8-24).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the teaching of Lam by substituting fibroblasts with genetically engineered fibroblast cells in view of Naughton. One would have been motivated to do so to produce recombinant protein in the skin construct (bioreactor system). Furthermore, it would have been obvious to one ordinary skill in the art to modify the skin construct of Lam by incorporating dermal papilla of hair follicles in view of Naughton. One would have been motivated to do so induce hair growth at site of skin implant. In addition a method for transplantation or implantation of a skin construct as taught by Lam is obvious in view of Naughton who teaches the technique of skin biopsies and transplantation. On would have been motivated to do so to promote wound healing in transplanted patients. One would have a reasonable expectation of success in doing so because genetic engineering of fibroblast host cells, substitution of a cell type in a skin construct and transplantation of skin construct is not only well within the reach of one ordinary skill in the art but also has been routine in the art.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300.**

Sumesh Kaushal
Examiner GAU 1636

SUMESH KAUSHAL
PATENT EXAMINER